UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
[illegible]	09/24/97	ECKSTEIN	F 228213

EXAMINER	
WANG, A	
ART UNIT	**PAPER NUMBER**
1635	29

DATE MAILED: 12/18/00

320306 HM22/1218
[illegible] BOEHNEN HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
[illegible] IL 60606

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER OF
PATENTS AND TRADEMARKS
Washington, D.C. 20231

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 29

Date mailed
12/18/00

Application Number: 08/936,657
Filing Date: 24 September 1997
Appellant(s): Eckstein et al.

Daniel A. Boehnen and Lisa M.W. Hillman
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed 15 November 2000.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The rejection of claims 44-57 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

No prior art is relied upon by the examiner in the rejection of the claims under appeal.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 44-57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is drawn to a method of cleaving any RNA via any ribozyme motif wherein the ribozyme is composed of at least one modified nucleotide, the modification comprising any modifier group replacing the 2' hydroxy of the ribose sugar. Further dependent claims limit the claimed invention to where the modifier group is any halo or any amino, and where the target RNA is viral. The context of the cleavage is not specified by the claim and thus reads broadly on ribozyme cleavage in any in vitro and in vivo context.

The specification as filed teaches only ribozymes with modified nucleotides having 2'-halo and 2'-amino cleaving RNA, and with cleavage of HIV LTR RNA in a cell free system. No ribozyme cleavage in cells is taught, although a stability against nuclease degradation for the ribozymes in cells in culture was conducted. No accompanying data on target cleavage

was mentioned or provided. No other guidance is provided for delivery of ribozymes to cells to cleave targets in any context is provided. No guidance is provided as to what other modifier groups and at what positions in ribozyme motifs such modifiers can be tolerated and provided for in a functional ribozyme, and further, one that could be delivered to cells in culture or in vivo (whole organism) and still further cleave target.

Note the state of the art for the construction of ribozyme which may be delivered and cleave targets in cells in culture and in a whole organism remain highly unpredictable due to RNA secondary and tertiary structure and the corresponding ability of the target to be accessible in cells, and the issues concerning delivery to cells (see Branch). The specification as filed fails to provide any general or particular guidance to resolve the unpredictable factors concerning the engineering and delivery of ribozymes to cleave targets in cells.

Several areas of de novo experimentation would have to be engaged to practice the invention as broadly claimed. To the extent that the ribozymes of the claims are drawn to having any modifier, no guidance is provided as to what other modifiers would be applicable and where within any catalytic motif of any ribozyme. Each ribozyme motif have core positions for which substitutions will not be tolerated. Furthermore, the ribozyme must be engineered such that they would cleave any target in any context. No guidance is provided in the specification as filed for the determination of every or any ribozyme cleavage site, even for any viral target RNA. Still further, the method claims call for cleavage to occur in any context in vivo. No general delivery schemes are known for ribozymes, and further for those

with modifier groups, such that they may find and cleave targets. All appellants have done is shown nuclease resistance in cells, but do not show that the ribozymes claimed, even for those shown in vitro, can cleave targets in cells, or further be delivered and cleave targets in a whole organism. To do so as claimed and recited in this paragraph would require undue trial and error experimentation since the specification as filed fails to provide any guidance in the known unpredictable factors concerning the engineering and delivery of ribozymes for cleavage of a desired target in cells.

(11) Response to Argument

Appellant's arguments filed November 15, 2000 have been fully considered but they are not persuasive. Appellants assert that the specification, as filed, provides guidance on the synthesis of modified ribozymes comprising halo, sulfhydryl, azido, amino, monosubstituted amino, and disubstituted amino modifications at the 2' sugar position, which is accurate insofar as to oligonucleotide synthesis since a ribozyme is an oligonucleotide but the asserted guidance does not enable the synthesis of an "active" ribozyme, having catalytic activity, as was discussed in the enablement rejection. Without specific guidance regarding nucleotide modifications at specific positions within a ribozyme sequence, the skilled artisan would have to engage in undue trial and error experimentation to determine which positions can be modified with a particular modifying moiety so that an active ribozyme can be synthesized. Furthermore, appellants' assertion that the specification does teach specific ribozyme positions that can be modified (paragraph bridging pages 6-7 of Brief) is not persuasive since said

guidance, found in pages 8-9, is merely conjecture without any evidence as to actual activity of such a modified ribozyme. Moreover, appellants arguments and declaration concerning the selection of target sites in a particular RNA species misplaced since the actual selection of target sites is not in question but rather the synthesis of an active ribozyme which can cleave any target RNA.

Appellants' arguments concerning the in vivo and in vitro delivery and applications of the disclosed ribozymes is also not found persuasive since the Stinchcomb declaration relies upon references which were post filing date references or references without publication dates, using methods not supported by the instantly filed specification. Such references would not provide evidence of enablement at the time of invention unless supported by the instant specification. For instance, Appellants cite exhibit 2, Flory et al., which discloses the in vivo application of ribozymes using direct intra-articular injection into the synovium of rabbit knees; exhibit 10, Lyngstadaas et al., which discloses direct mandibular injection of ribozymes into newborn mice; and exhibit 3, Ayers et al., which discloses intraocular delivery using polyacrylic acid, for support of an enabling specification but as noted above said in vivo delivery methods is not supported by the instantly filed specification. Furthermore, Flory et al. clearly states that "there are no reports that demonstrates the efficacy of synthetic, stabilized ribozymes delivered in vivo" thereby providing further support that the Appellants were not in possession of the claimed invention to have possibly enabled the invention as broadly claimed. Moreover, the Ayers et al. merely describes a method of delivering a ribozyme, in vivo,

without providing any evidence pertaining to efficacy of the ribozyme in any treatment methodology.

Appellants also assert that exhibit 1; Christoffersen et al. and exhibit 6; Beigelman et al., further demonstrate the in vivo use of modified ribozymes but contrary to appellants' assertions, Christoffersen et al.'s and Beigelman et al.'s disclosures are not relevant to in vivo applications since there is no nexus between a transfection in culture and in vivo therapy.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Andrew Wang
December 13, 2000

ANDREW WANG
PATENT EXAMINER
TC 1600

REMY YUCEL, PH.D
PRIMARY EXAMINER

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Conferee

MCDONNELL, BOEHNEN, HULBERT & BERGHOFF
300 South Wacker Drive
Chicago, IL 60606